Decision Memo for Actinic Keratoses (CAG-00049N)

Decision Summary

The *Coverage Issues Manual* will be revised to indicate that Medicare will cover the destruction of actinic keratosis, without restrictions based on lesion or patient characteristics, using surgical or medical treatment methods, including but not limited to:

- cryosurgery with liquid nitrogen,
- curettage,
- excision, and
- photodynamic therapy.

CMS expects that practitioners will maintain sufficient information, as required under 42 CFR § 424.5(a)(6), to enable them to demonstrate entitlement to Medicare reimbursement for covered procedures and services.

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Decision Memo

(The information contained here represents only the first step towards making coverage of these services effective. A manual instruction must be prepared and approved, and the necessary billing and claims processing instructions must be prepared. In addition, changes must be made to bill processing systems in order to allow payment to be made. Consequently, the effective date of service will not be known until the manual instruction has completed the clearance process and been assigned an effective date.)

TO: Administrative File CAG-00049N : Management of Actinic Keratosis

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SUBJECT: National Coverage Determination
DATE: July 19, 2001

This memo serves four purposes: (1) describes actinic keratosis (AK) and methods of managing this skin lesion; (2) reviews the history of Medicare's coverage of management of actinic keratosis and provides a timeline of recent activities; (3) presents and analyzes the relevant scientific and clinical data related to actinic keratosis; and (4) delineates the reasons for making a positive national coverage decision.

Clinical Background

Actinic keratoses (AKs), also known as solar keratoses, are common, sun-induced pre-cancerous skin lesions that are confined to the epidermis. The lesions typically appear as circumscribed, rough, scaly patches on sun exposed skin, ranging from flesh-colored to reddish-brown. Due to their distinctive roughened quality, AKs may be easier to detect by palpation than visualization (especially in the early stages of development). AKs are usually 1 to 3 mm in diameter, but may be larger in size and may appear in clusters.

AKs are dynamic in nature. Although most AKs are asymptomatic, some may exhibit signs and symptoms such as thickening, burning, tenderness, or itching. AKs may also progress to squamous cell carcinoma (SCC), a form of skin cancer. This progression may or may not be related to the development of signs and symptoms, and the scientific evidence related to AK progression is discussed more thoroughly in the Summary of Evidence section of this document. Finally, AKs can also regress. In two studies, the rates of AK regression were 21% and 25.9% a year[1]. In a third study, rates of regression were reported for prevalent and incident AKs. Prevalent AKs (those that were present on the first examination) exhibited a regression rate of 74% while incident AKs (those developing following the initial examination) regressed only 29% of the time[2]. Over the course of one year, however, 15% of AKs that regressed were found to later recur. This raises concern that the regressed AK may still be present, but not appreciable on examination.

AKs are most prevalent in fair-skinned individuals with a history of significant sun exposure. The prevalence of AKs increases with advancing age, and AKs are more common in men than women. AKs are more common in immunosuppressed patients and in patients with some genetic disorders (such as xeroderma pigmentosum). In five studies on AK (using either a random or a population-based sample), the overall reported prevalence of AKs ranged from 23-61.1%[3]. In these studies, the reported annual incidence of AK ranged from 12.6-43.4%[4]. These rates of prevalence and incidence demonstrate a clear relationship to geographic location, as the lower rates were reported from a study conducted in Wales and the higher rates reported from several studies in Australia. Due to these high rates of prevalence and incidence, destruction of AKs is the most commonly performed outpatient dermatologic procedure in the United States[5].

The available literature on AK suggests that this issue is particularly relevant to the Medicare population. Frost, et al. (2000) reported 83% prevalence of AKs in Australian men aged 60-69 years. However, this reported prevalence rate is impacted by geographic region, as sun exposure in the Australian population is likely higher than most areas in the United States.

A search of Medicare data by the Oregon Health & Science University (OHSU) indicated that 6.7-9.1% of beneficiaries over age 65 were treated for AKs between 1991 and 1995[6]. These treatment percentages are likely lower than the actual prevalence of AKs in the Medicare population, as OHSU reports that "...only a small proportion of individuals with AKs seek or receive treatment"[7].

Management Options

Various options exist for managing AKs, and clinicians may consider several factors to determine the most appropriate management strategy, including size, location or growth pattern of the lesion, patient preference, and patient medical history. Common treatments for AK include cryosurgery with liquid nitrogen, topical treatments, and curettage. Other less common treatments for AK include dermabrasion, excision, chemical peels, laser therapy, and photodynamic therapy (PDT)[8]. An alternative approach to the management of AKs is watchful waiting, such that lesions are removed only when they exhibit specific clinical features suggesting possible transformation to invasive SCC.

Cryosurgery with liquid nitrogen, the most common treatment for AKs in the U.S., is most appropriate when discrete AKs are present. With this procedure, liquid nitrogen is applied directly to AK lesions as a method of destruction. The procedure generally does not require the use of a local anesthetic and involves only mild pain and minor side effects, such as temporary post-procedural erythema.

Topical treatments, such as the chemotherapeutic agent 5-fluorouracil (5-FU), are most commonly used for patients with multiple lesions. The 5-FU cream is applied to the entire region that is affected, and the recommended course of treatment involves several applications per day over a 2 to 4 week time span. 5-FU selectively targets the damaged skin, causing an inflammatory response with erythema, necrosis, and erosion. Numerous side effects are associated with 5-FU, including pain or irritation, tenderness, ulceration, burning, and inflammation. As a result, patient compliance is a significant concern with this treatment.

Curettage, which involves the use of a curette to scrape away the lesion, is another common method of treatment for AKs. In some instances, curettage may be used in combination with electrosurgery to stop bleeding or apply more damage to the affected area. The primary advantage of curettage is the ability to submit the specimen for histologic analysis, particularly in cases where invasive squamous cell carcinoma is suspected. Disadvantages of curettage include the need for local anesthesia and the potential for scarring.

Photodynamic therapy (PDT) represents an emerging technology in the treatment of AKs. PDT uses the topical agent 5-aminolevulinic acid (5-ALA) to selectively photosensitize the atypical cells of the AK lesion. Approximately 14 to 18 hours following application of the 5-ALA, the skin is exposed to a light source and the cells of the AK lesion are destroyed. Common side effects of PDT include erythema, stinging/burning, edema, and scaling or crusting of the lesion. The primary disadvantage of PDT is the need for treatment over a 2-day period.

FDA Approval

Each of the AK treatment options discussed in the previous section has received FDA approval. Since the 1960's, cryosurgery with liquid nitrogen has been routinely used for multiple medical indications. As a result, early clearance for cryosurgery was granted for general tissue destruction. In 1980, Cryomedics, Inc. received FDA clearance under the 510(K) process for the Krymed Liquid Nitrogen Cryojet, with destruction of AKs as a specific clinical indication (among several other dermatologic indications). Since 1980, there have been several additional cryosurgery devices cleared for dermatologic use.

In 1970, 5-FU (tradename Efudex®) was reviewed under the New Drug Application (NDA) process and determined to be safe and effective for the topical treatment of actinic or solar keratoses. Three different Efudex® products were approved for treatment of AKs: 2% fluorouracil topical solution, 5% fluorouracil topical solution and 5% fluorouracil topical cream. In October 2000, Dermik Labs received NDA approval for a generic 0.5% fluorouracil topical cream.

One PDT system currently has approval for the treatment of AKs. In 1999, DUSA Pharmaceuticals, Inc. received FDA approval for Levulan® Kerastick™. Levulan® Kerastick™ involves the use of both a drug (20% ALA topical solution) and a device (the Levulan® Kerastick™ for application of ALA and the BLU-U™ Illuminator as the light source). Levulan® Kerastick™ received premarket approval (PMA) as a photodynamic therapy system "...for the treatment of non-hyperkeratotic actinic keratoses of the face or scalp"[9]. No other PDT system currently has FDA approval for the treatment of AKs.

History of Medicare's Coverage on AK Management

Presently, Medicare has no national policy with regard to the management of AK. In the absence of a national coverage policy on AK management, several Medicare contractors have developed local policies on AK and these local policies vary significantly.

Between 1998 and 1999, several contractors implemented local policies that limit removal of AKs to lesions that exhibit one or more of the following characteristics:

- are symptomatic and exhibit features suggestive of possible malignant transformation (e.g. bleeding, itching, pain, inflammation, notable change in size or color, etc.),
- are located on high risk anatomic sites (e.g., lips, ears, nose, eyelids, or a previous burn site),
- have failed to respond to topical chemotherapeutic agents, or
- occur in individuals with a high risk of malignant transformation (e.g. individuals with chronic immunosuppression, previous exposure to ultraviolet therapy, prior history of skin malignancy, prior exposure to arsenicals or radiation, etc).

Some other local policies, however, characterize AKs as precancerous lesions with the potential to progress to invasive SCC and allow routine treatment. In 2000, however, several of these policies limited the number of treatment sessions to four per year, unless further documentation is provided to justify additional treatments. Finally, some local contractors have no written policy on the treatment of AKs. In these instances, claims are subject to medical necessity determinations on a case by case basis.

Current Request

In December 1999, the Centers for Medicare & Medicaid Services (CMS), formerly known as the Health Care Financing Administration (HCFA), received a formal request for coverage consideration on treatment of AK from the American Academy of Dermatology Association (AADA). In January 2000, AADA representatives emphasized their concern regarding the inconsistencies that exist in various local medical policies on AK treatment. CMS offered to assist the AADA in working with the CMS Program Integrity Group to open a dialogue with various Medicare contractors in order to try to resolve some of the issues related to the treatment of AKs. In March 2000, CMS received a communication from the AADA requesting that their formal request for coverage consideration be placed on hold. In June 2000, CMS received a communication from the AADA requesting that the formal request be re-opened, thus beginning the formal coverage consideration process.

Timeline of Recent Activities

June 6, 2000	Received a letter from the AADA requesting that CMS re-open their formal request.
August 15, 2000	CMS notified the AADA that CMS has requested a technology assessment from the Agency for Healthcare Research and Quality (AHRQ).
May 8, 2001	Received technology assessment from AHRQ.
May 29, 2001	AADA representatives met with CMS to present additional information related to the findings of the technology assessment.

Summary of Evidence

Problem Formulation

In order to address the issue of managing AKs in the context of Medicare policy, CMS formulated the following questions:

1. *Is there adequate evidence to support the routine removal of AKs in contrast to a strategy of watchful waiting?*

2. *If #1 is YES, is there adequate evidence to select lesions for routine removal which have particular anatomic characteristics predisposing such lesions to SCC?*
3. *If #1 is YES, is there adequate evidence to select patients for routine removal of AKs who have certain high-risk characteristics predisposing them to SCC?*
4. *If #1 is YES, is there adequate evidence to demonstrate the differential efficacy of any particular treatment modalities?*

Review of Evidence - Technology Assessment

In August 2000, CMS requested a technology assessment from the Agency for Healthcare Research and Quality (AHRQ) to review and assess the literature on incidence, treatment, and progression of AKs. AHRQ selected the Evidence-based Practice Center (EPC) at the Oregon Health & Science University (OHSU) to develop the evidence report. An EPC performs systematic reviews of the literature on a clinical topic to form evidence-based conclusions. Key questions for the technology assessment on AK, which are very similar to the above problem formulation questions, were developed by CMS, in consultation with AHRQ. Following a review by representatives of dermatologic professional societies, OHSU further refined the key questions and used them to guide development of the report. To view the key questions and final assessment for AK, see the attached Technology Assessment (PDF, 433KB).

The conclusions of the technology assessment are described below, with supplemental analyses performed by CMS staff where pertinent, in the context of the key questions delineated above. The assessment did not address AKs on the lip, ear, eyelid, or in immunocompromised patients, as there is consensus that AKs should be removed routinely in these instances, due to relatively higher rates of progression to metastatic SCC[10].

Question 1 - Is there adequate evidence to support the routine removal of AKs in contrast to a strategy of watchful waiting?

The argument supporting routine treatment of AKs relies upon the assumptions that:

- AKs are precancerous lesions,
- some AKs will progress to invasive SCC, and
- treating AKs will prevent development of invasive SCC.

Assumption 1 - AKs are precancerous lesions

Based on the histologic properties of AKs and SCCs, AKs have commonly been identified as precancerous lesions. Histologically, AKs are identified as atypical cells confined to the epidermal layer of the skin, while SCC is diagnosed when the atypical cells involve the dermis. Thus, the histologic difference between AK and SCC is primarily the extent and location of atypical cells, and there appears to be consensus within the literature that AKs can progress to SCCs.

The similarity between AK and SCC lesions is supported by studies examining the accuracy of clinical diagnoses of AK and SCC. Three studies reported in the technology assessment compared the clinical diagnosis of AK with pathologic results following a biopsy. The reported accuracy of clinical diagnosis ranged from 81-94% in these studies[11]. Two studies of interobserver agreement showed moderate to poor agreement on diagnosis of AK[12]. One of these studies compared interobserver agreement between dermatologists while the other compared the diagnosis of a general practitioner to that of a dermatologist. Neither study submitted AK lesions for histopathological analysis to confirm clinical diagnoses.

Several studies indicated that the clinical diagnosis of SCC is less reliable than that of AK[13]. In one study, dermatologists correctly diagnosed SCC only 51% of the time, with surgeons and general practitioners demonstrating even lower diagnostic accuracy[14]. In practice, AKs are frequently not subject to histopathological evaluation, but rather are treated on the basis of clinical examination alone.

However, a debate exists within the medical community over whether AKs should be identified as "precancerous lesions" or as "true cancers". Proponents of the view that AKs represent a true cancer argue that AKs and SCC represent a continuum, and that it is difficult, if not impossible, to distinguish when the "cancer" begins. Such proponents argue that the atypical cells presenting as an AK are indistinguishable from the atypical cells of SCC and also point to molecular similarities between AKs and SCCs, specifically the presence in both of a mutation of the p53 gene. This genetic link provides evidence that "...AK represents the beginning of the SCC continuum"[15].

In contrast, those who support the notion that AKs are a precancerous lesion emphasize the behavior of the lesion, noting that AKs frequently regress, do not grow actively, and do not have the potential to metastasize. They also note molecular similarities between AKs and sun-damaged skin without dysplasia.

Despite this ongoing dialogue regarding the nature of AKs as "precancerous" versus a "true cancer", there appears to be a consensus that AKs and SCCs are linked histologically. Further research is necessary to determine the specific mechanism of progression from an AK to invasive SCC and the malignant transformation of some SCCs.

Assumption 2 - Some AKs will progress to SCC

Some evidence exists to support the assumption that some AKs will progress to SCC. As discussed earlier, AKs and SCCs are linked histologically, with the diagnostic difference existing mainly in location and degree of atypia of the cells. In addition, several studies have demonstrated that the presence of AKs is more strongly associated with the development of SCC than other factors, including age, gender, and skin type[16].

There are few sources of data to predict the rate of progression from AK to SCC. The technology assessment reported two well-conducted studies in Australia that reported a yearly progression rate of 1-2 SCCs per 1000 AKs[17]. However, only one of these two studies actually linked SCCs to a specific, pre-existing AK. CMS staff conducted a further analysis of these articles.

Both studies reported on a subset of a 5-year longitudinal study in Maryborough, a small Australian city. Investigators invited all residents of the city 40 years and older to attend an annual dermatological exam over a 5 -year period.

In the first of these studies[18], participants were examined by a team of experienced clinicians, and all clinically diagnosed AKs were noted. Participants were instructed that no AK treatment was necessary unless they noted lesion changes. 1,040 residents were examined in 1983, with a mean age of 58.8 years. On initial exam, 424 participants had no AKs (40.8%) and 616 (59.2%) had at least one. There were 4,746 AKs identified in the 616 participants with at least one AK (7.7 per person on average). During the course of the year, 3 of the 616 had lesions treated, thus 613 were available for analysis.

At the 1-year mark, 12 of 1037 participants[19] developed a total of 14 SCCs. Of the 613 who had AKs and no treatment, 10 people developed a total of 11 SCCs (11 SCCs/613 participants, 1.8%). Of the 424 who had no initial AKs, 2 people developed a total of 3 SCCs (3 SCCs/424 participants, 0.7%). For every SCC that occurred, there were 429 AKs, resulting in an annual incidence rate for SCC of 0.24% for every lesion present at the first interview.

The second study represented a continuation of the Maryborough study discussed above, utilizing similar methodology[20]. However, this study attempted to grid specific AK lesions to measure specific patterns of progression. In this study, 1689 participants were seen on 2 consecutive years (4267 occasions) over the study period. On 2606 (61%) of these occasions, subjects exhibited at least one AK. On 28 separate occasions, a SCC had developed by the second visit (26 people).

Ten SCCs occurred at the site where an AK had been recorded, while 7 arose on clinically normal skin. In the other 11, the investigators could not determine whether the SCC arose from a previous AK, either because the patient had received treatment or the notes did not make it clear whether the SCC occurred in or adjacent to a pre-existing AK. Regardless of location, the rate of transformation was approximately 1/1000.

Finally, the study reported that the mean number of AKs present at the first of the 2 visits was significantly greater in those people in whom a SCC developed (16.9) than in those without SCC (5.1), $p < 0.001$. This finding indicates that individuals with multiple AKs may incur a higher risk of SCC development than those with fewer AKs.

In summary, several studies have demonstrated an association between the presence of AKs and the development of SCCs, and two studies suggest a progression rate of 1-2 SCCs per 1000 AKs. Further, the second of these studies provides preliminary evidence to demonstrate progression of specific AKs to the subsequent occurrence of SCC.

Assumption 3 - Treating AKs will prevent development of SCCs

As indicated in Assumption 2, the presence of AKs in an individual may be a significant predictor for SCC occurrence. Therefore, it seems logical that treatment of AKs can help prevent the development of SCC. However, AKs could be a marker for people at increased risk of SCC in general, in addition to being a precursor lesion. Unfortunately, there is virtually no direct scientific evidence to determine which assumption is correct.

Only one study examined the impact of AK treatment on subsequent development of SCC. In this case series study, the clinical records of 23 patients requiring "frequent visits for treatment of multiple new [AK] lesions" were reviewed for the appearance of AKs and/or SCCs following full face or partial face dermabrasion[21]. After 1 year, 22 of the 23 patients had no AKs and 19 of 23 patients exhibited no AKs after 2 years. In the 3rd year of follow-up, 15 of 19 patients were free of AKs and 9 of 14 exhibited no AKs in the 4th year. The study reported no occurrence of SCC after 4 years of follow-up.

In evaluating the dermabrasion study, OHSU assigned a rating of "Fair Minus"[22], citing "low or uncertain follow-up rates" as the reason for the rating. In addition, CMS's analysis of the article identified concerns related to small sample size, lack of details regarding selection criteria for patients, minimal discussion of exclusion criteria, and absence of intention to treat analysis. Further, the lack of a control makes it difficult to meaningfully interpret these results.

The technology assessment reported no other studies on preventing progression of AK to SCC. Additional studies discussed below focused on the ability of a specific treatment method to reduce the number of AK lesions per patient, but did not go further to examine SCC occurrence. No studies compared observation/monitoring of AKs with selective removal of AKs and/or aggressive treatment of multiple AKs.

In one case series, treatment with cryosurgery resulted in a recurrence rate of only 1.2% for 70 patients followed over 1-8.5 years[23]. An additional case series examined the efficacy of 5-FU, used 1-2 days per week over an average of 6.7 weeks. Eighty-six percent of AKs reportedly cleared in the first 6 of 11 patients to reach a 9-month post treatment follow-up[24]. Finally, in a case series examining the use of a chemical peel referred to as "cryopeeling", 373 patients with a total of 34,604 AKs were examined 6 months after treatment. At 6 months, 90% of patients were available for follow-up, exhibiting a 4% recurrence rate[25].

In 2 controlled trials, the topical retinoid tretinoin was found to reduce the number of AKs more effectively than placebo (vehicle cream) after 3-4 months of treatment[26]. An additional pilot study compared PDT (10%, 20%, and 30% ALA) to placebo. Overall, 50% of AKs treated with ALA had a complete response versus 3% of AKs treated with placebo[27]. Another controlled trial assessed the efficacy of a superficial chemical peel (glycolic acid), reporting a reduction in the mean number of AKs from 13.7 to 11.6 at a 6-month follow-up visit[28].

Finally, a controlled trial comparing PDT (20% ALA) to placebo in 243 patients reported that 88% of patients had a reduction of at least 75% of AKs after 12 weeks[29]. It is important to note, however, that these results were reported in a review article and the study has not been published in a peer-reviewed journal. Four additional controlled trials compared 5-FU (the control) with other treatment methods, and these studies are discussed in detail under Question 4 below.

In summary, the evidence related to the above three assumptions indicates that AKs are histologically linked with SCCs, AKs can infrequently progress to SCC and, thus, treating AKs may reduce the incidence of SCCs. However, this final link in the causal chain is not supported by direct evidence.

Question 2 - If #1 is YES, is there adequate evidence to select lesions for routine removal which have particular anatomic characteristics predisposing such lesions to SCC?

As stated earlier, the technology assessment did not address AKs located on the lip, ear, or eyelid, due to their association with relatively higher rates of progression to metastatic SCC and the consensus that such lesions should be routinely removed. Although characteristics such as burning, itching, pain, hyperkeratosis, or bleeding are sometimes thought to be high-risk markers, the technology assessment did not identify any studies that measured the ability of lesion characteristics to predict AK progression to SCC.

Question 3 - If #1 is YES, is there adequate evidence to select patients for routine removal who have certain high -risk characteristics predisposing them to SCC?

The technology assessment also did not address AKs occurring in immunocompromised patients (such as transplant patients). Again, this was based on the consensus that AKs should be removed routinely in these patients due to a relatively higher risk of progression to metastatic SCC. Beyond this patient category, prior patient history of skin cancer has also been linked with a higher likelihood of subsequent SCC occurrence. The technology assessment identified one large, prospective, randomized trial that examined the use of retinol to prevent skin cancer. In this study of 2297 Arizona residents who had at least 11 AKs, the strongest risk factor for developing SCC was a prior history of skin cancer[30].

Question 4 - If #1 is YES, is there adequate evidence to demonstrate the differential efficacy of any particular treatment modalities?

The studies in this section were included in the OHSU technology assessment, but were subjected to additional HCFA staff analysis. Four controlled trials have been conducted to compare 5-FU (the control) with other treatment methods. Bercovitch (1987) compared the use of 5% 5-FU with 5% 5-FU plus tretinoin cream in a double-blind, randomized trial. Twenty participants all had multiple AKs on the forearms and hands, and 5-FU was self-administered to both the forearms and hands twice daily. Following 5-FU application, .05% tretinoin cream was randomly applied to one side (treatment) and a placebo cream (control) to the other. The number of AKs were counted prior to treatment and at a 12-week follow-up session. Nineteen of the original twenty participants were available for assessment at the 12-week follow-up session.

This study reported a 78% reduction in AKs in the treatment side versus 73% reduction in AKs on the control side. Both responses were statistically significant at $p < .04$. The report also indicated a statistically significant difference between the 2 treatment responses, but the level of significance was not reported. There were several limitations with this study, including small sample size, lack of information on selection criteria (e.g., unclear use of consecutive patients), varying length of treatment per patient based on tolerance, lack of detailed information on blinding method, and lack of information on assessment of patient compliance with treatment.

Simmonds (1973) compared the effectiveness of 1% and 5% 5-FU in removing AKs on the face. Sixteen participants self-administered 1% 5-FU cream to the right side of the face and 5% 5-FU cream to the left side of the face, though participants and researchers were blinded to this distribution. Results of this study reported "...no difference in treatment time or degree of efficacy for either the 1% or 5% fluorouracil topical cream". Study limitations included small sample size, unclear criteria for judging response to treatment, and the omission of numerous methodological design characteristics (including selection criteria, clinical assessment criteria, etc.).

In 1999, Kurwa, et al. conducted a study to compare 5-FU (5%) to PDT (5-ALA followed by irradiation with a halogen lamp emitting red light). Seventeen patients with a long history of AKs on the forearms and hands were initially recruited for this study, and patients were randomized to apply 5-FU (twice daily for 3 weeks) to one hand and receive PDT to the other hand. Clinical margins of the AKs on both hands were traced prior to treatment and at 1 week, 4 weeks and 6 months following the start of treatment.

Fourteen of the original seventeen patients completed the study and the mean lesional areas were compared pre- and post-treatment. The study reported a mean lesional reduction of 70% for lesions treated with 5-FU and a 73% reduction in lesions treated with PDT after 6 months of follow-up. The difference in response to the two treatments was not statistically significant. No patients exhibited a complete destruction of AKs with either treatment. Limitations included small sample size, lack of information on selection criteria, lack of information on assessment of patient compliance with 5-FU, and non-blinding study design. Further, results at 1 and 4 weeks of follow-up were not reported.

A fourth study of 5-FU was reported in two different articles. Lawrence, et al. (1995) initially reported on a study comparing a medium-depth chemical peel (Jessner's solution and 35% trichloroacetic acid) to 5% 5-FU in 15 patients. Following a daily self-administration of 0.025% tretinoin cream to both sides of the face for 2 weeks, each patient was subjected to the chemical peel on the left side of the face and 5-FU to the right side of the face. AKs were counted prior to treatment and at 1, 6 and 12 months following treatment.

Twelve of the fifteen patients completed the 12-month study, and reported results indicate that "both fluorouracil [5-FU] and the chemical peel induced almost identical percent reductions (75%) in the number of AK". The study reports that this reduction in AKs was noted at the 1-month follow-up and persisted throughout the 12-month study period. As with earlier studies, methodological flaws included non-blinding study design, small sample size, lack on information on selection criteria and characteristics of the study setting, and a lack of information on whether patient compliance with 5-FU was assessed. Further, the results at 6 and 12 months of follow-up are confounded by intervening treatment of persistent AKs (35% trichloroacetic acid and cryosurgery at 6 months, shaving at 12 months).

Witheiler, et al. (1997) later reported a 32-month follow-up on the patients from the Lawrence study. Results indicate an increase in the mean number of AKs between 12 and 32 months. However, this study contained flaws in addition to those of the Lawrence study, including the availability of only 8 patients for follow-up and intervening treatment of some AKs during the study period (between 12 and 32 months).

Finally, the technology assessment reported one additional article comparing the use of two different medium depth chemical peels (70% glycolic acid versus Jessner's solution prior to 35% trichloroacetic acid)[31]. The study utilized a split face paradigm[32] in 13 male patients with "photodamaged facial skin". Patients were advised to self -administer 0.05% tretinoin cream nightly for 2 weeks prior to the chemical peel. Photographs of the patients were taken prior to and 60 days following the chemical peel. Based on these photographs, the clinical improvement of each side of the face was graded by 3 reviewers on a scale from 0 to 3.

The reported results of this study indicated that the glycolic acid peel (grade of 1.58) was slightly more effective than the Jessner's peel (grade of 1.33) in removing AKs. Both ratings fell in between "fair" and "good", and level of significance was not reported. Again, methodological flaws included small sample size, lack of information on rating criteria, lack of information on selection criteria, absence of a discussion of patient characteristics (e.g. number of AKs per patient, number of patients with AKs), and a lack of information on blinding and randomization procedures. No additional articles on comparative therapeutic efficacy were provided in the OHSU assessment.

Position Statements and Clinical Guidelines

American Academy of Dermatology Association

The American Academy of Dermatology Association (AADA) initiated CMS's formal consideration of coverage for AK in a letter to the Administrator. In this letter, the AADA stated their position that "...a policy that limits treatment of AKs entirely or defers treatment until invasive SCC arises is unnecessary and wrong." The AADA supports a uniform, national Medicare coverage policy that "...is medically appropriate, scientifically sound, protects Medicare beneficiaries from the risk of developing SCC, and allows them to receive the best, most cost-effective treatment for their disease."

Further, the AADA's Committee on Guidelines of Care developed a report in 1995 detailing guidelines of care for AK[33]. The guidelines characterize AKs as premalignant lesions with the potential to develop into SCC and state that "...it is incumbent on all practitioners to provide efficacious, cost-effective therapy." The report details the wide variety of treatment methods for AK and indicates that the method selected depends on a variety of variables (including medical status of the patient, lesion characteristics, etc.). The report states, further, that "observation may be acceptable in certain informed patients" but concludes, "the ultimate judgement regarding the propriety of any specific procedure must be made by the physician in light of all the circumstances presented by the individual patient." Recently, the AADA has sent additional communication to CMS, reinforcing their position that Medicare should issue a national coverage policy for the treatment of AKs.

The Skin Cancer Foundation

In 1998, The Skin Cancer Foundation submitted a letter to CMS indicating their objection to any "...proposed restrictions on the treatment of actinic keratoses by dermatologists." The letter further stated the position of The Skin Cancer Foundation that AKs evolve into skin cancer, but can be treated with little harm to the patient. The letter concluded that restricting the ability of the dermatologist to treat AK lesions is "entirely unjustifiable."

Additional Experts

The AADA's formal request for consideration, submitted to CMS, included over 50 letters from dermatology professors and department chairs at major universities and hospitals across the country. These letters all expressed the belief that AKs are premalignant lesions warranting routine treatment. Further, the letters urged CMS to implement a policy that does not place restrictions on treatment (based either on lesion characteristics, patient characteristics, or treatment type).

Other Countries

Finally, following a request from CMS, AHRQ searched an international database and found no other technology assessments on the management of AK. Given the high prevalence of AK in Australia, HCFA also reviewed Australian policy on the management of AK. Treatments for AK are covered by the Australian healthcare system, with NCDs on type of treatment left to the discretion of the physician.

CMS Analysis

In addition to the technology assessment, this analysis takes into consideration the position statements of specialty societies, expert opinion of physicians, an internal review of Medicare utilization data, and all other information received by the agency on this topic. CMS also conducted an internal review of several articles included in the technology assessment, as well as additional articles submitted to the agency or identified through an internal literature search.

Question One

Overall, the body of **direct** scientific evidence to support routine treatment of AKs is small. Only one study has attempted to link the progression of specific AKs to the development of SCC, and only one case study on dermabrasion attempted to assess the impact of AK treatment on subsequent development of SCC. In addition, while a few studies have been conducted to examine the effectiveness of treatments in reducing the number of AKs, the studies tend to be small and are often case series. Further, the controlled trials that exist have not consistently included blinding, randomization and comparison of treatment methods to a placebo group. Despite these limitations, this small body of literature provides preliminary direct evidence indicating that AKs can progress to SCC and that treatment can reduce the number of AKs and possibly SCCs.

CMS has also taken into consideration several factors that offer **indirect** support for routine treatment. First, as discussed previously, several studies have demonstrated that the presence of AKs is more strongly associated with the development of SCC than most other factors. Based on this association of AKs and SCCs, CMS concludes that treatment of AKs may be warranted to prevent the risk of developing an invasive SCC.

Further, CMS concludes that the reported annual progression rates of 1-2 SCCs per 1000 AKs, when used to support a watchful waiting strategy for the treatment of AKs, may not reflect the actual long-term risk to the patient. With such a monitoring strategy, AK lesions that do not suggest the presence of malignant transformation would not be treated. Since it is likely that some of these asymptomatic lesions would endure in a given patient beyond 1 year, the reported annual rates of progression may not reflect a true risk to the patient. The true long-term risk to the patient is difficult to predict. Mathematical models reported in the technology assessment that attempt to extrapolate beyond an annual rate of progression contain several limitations, including assumptions of average number of lesions per patient and constant rates of progression.

The reported results of poor clinical accuracy for the diagnosis of SCC also raise concerns related to an AK management strategy of watchful waiting. Without routine treatment of AKs, the potential exists for a physician to misdiagnose a SCC as an AK, resulting in a delay in treatment of the SCC. As reported in the technology assessment, SCCs can and do metastasize, with reported rates of metastasis ranging from 0.5-16%[34]. Thus, misdiagnosis of SCC resulting in a treatment delay could potentially result in an increased morbidity and mortality from metastatic SCC.

Only one case series has attempted to examine whether a treatment delay was related to the likelihood of metastasis. In that series, 2.5% of metastatic tumors had a diagnostic delay time of less than a month and 35.3% had a delay of 1-6 months[35]. However, the reliability of this study is difficult to determine, as the report did not indicate how the delay was assessed. Without further evidence, it is impossible to predict the rate of progression from SCC to metastasis and the resultant risk incurred by a monitoring strategy for AKs.

In summary, the above factors indicate that there are some studies suggesting a link between AKs and the development of SCCs. However, the specific mechanism of transformation and rates of progression have not been definitively established. In addition, the few available studies suggest that AK treatment methods are efficacious and safe. CMS has also received strong, consistent, expert testimony from dermatologists and surgeons supporting the routine treatment of AKs to prevent invasive SCC. However, a debate appears to center around whether the AK lesion itself represents a cancerous or precancerous lesion. Finally, CMS acknowledges the potential risk to the patient if AKs remain untreated. The lack of direct scientific makes this risk impossible to quantify at this time.

Questions Two - Four

The relatively clear-cut absence of evidence to affirmatively answer these three questions does not warrant extended discussion. Question Four, in particular, highlights the need for additional studies that enable the relative efficacy of various treatments to be enumerated.

Conclusions

Individual clinical NCDs regarding the routine removal of AK are supportable via this review of the medical evidence. There is consensus that immunosuppressed individuals, people with a prior history of skin cancer, and people with AKs of the lips, nose, ear or eyelid are at increased risk of developing SCC. The available scientific evidence does not allow for the identification of additional lesion and/or patient characteristics that place individuals at a higher risk of developing invasive SCC.

Additionally, CMS concludes that high-quality studies do not currently exist to justify the use of one treatment method over another. As discussed earlier, different treatment methods may be warranted in different clinical situations (including, but not limited to, discrete versus multiple lesions, need for histological confirmation of the diagnosis, and patient compliance). Further, the available evidence does not allow a definitive conclusion regarding the risk to the patient of a watchful waiting treatment strategy. In fact, the AADA's guidelines indicate that an observation strategy may be an acceptable treatment approach in certain circumstances. We also conclude that the number of treatments required for patients with AKs cannot be derived from the clinical literature, although in general, most Medicare patients diagnosed with AKs are treated in 1or 2 visits.[36]

As indicated earlier, AKs are dynamic lesions with the potential to progress or regress. Not enough is known about the mechanism of transformation of AKs. Further research is necessary to assess the efficacy of various treatment modalities, to more firmly establish a direct link between AKs and SCC, and to assess the risk of progression from AK to SCC and SCC to metastasis. CMS would like to see larger, high-quality, randomized controlled trials designed to compare the effectiveness of various treatment methods. In addition, registry studies are needed to assess the morbidity and mortality related to SCC and to further establish the relationship between SCC and AK. Additional critical research priorities are discussed in the technology assessment.

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[1] Harvey I, et al. 1996; Marks R, et al. 1986

[2] Frost C, et al. 2000

[3] Frost C, et al. 2000; Harvey I, et al. 1996; Marks R, et al. 1986; Marks R, et al. 1988; Marks R, et al. 1989

[4] Frost C, et al. 2000; Harvey I, et al. 1996; Marks R, et al. 1986; Marks R, et al. 1988; Marks R, et al. 1989

[5] Fleischer A, et al. 1997

[6] Oregon & Health Science University technology assessment

[7] Oregon & Health Science University technology assessment

[8] Dinehart S 2000

[9] FDA PMA number P990019 found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?ID=4532

[10] Alam M, et al. 2001; DeVries N 1969; Petrovich Z, et al. 1987; Rowe D, et al. 1992

[11] Ponsford M, et al. 1983; Thompson S, et al. 1993

[12] Whited J, et al. 1995; Whited J, et al. 1997

[13] Ponsford M, et al. 1983; Hallock G, et al. 1998; Whited J, et al. 1995; Whited J, et al. 1997

[14] Nixon R, et al. 1986

[15] Leffell D 2000

[16] Green A, et al. 1990; English D, et al. 1998; Marks R, et al. 1988

[17] Marks R, et al. 1986; Marks R, et al. 1988

[18] Marks R, et al. 1986

[19] Final analysis excluded the 3 patients that received AK treatment during the study period.

[20] Marks R, et al. 1988

[21] Coleman W 1996

[22] To classify study quality, the OHSU technology assessment used criteria developed by the US Preventive Services Task Force (USPSTF). These criteria are presented in Appendix 2 of the technology assessment.

[23] Lubritz R, et al. 1982

[24] Pearlman D 1991

[25] Chiarello S 2000

[26] Alirezai M, et al. 1994; Misiewicz J, et al. 1991

[27] Jeffes E, et al. 1997

[28] Marrero G, et al. 1998

[29] Ormrod D, et al. 2000

[30] Moon T, et al. 1997

[31] Tse Y, et al. 1996

[32] In the split face paradigm, the face is divided into left and right halves and different treatments are applied to each half.

[33] Drake L, et al. 1995

[34] Dinehart S, et al. 1989

[35] Epstein E, et al. 1968

[36] CMS analysis of a 5% sample of Medicare claims data indicates that, in both 1997 and 1999, 93% of all beneficiaries in the data set were treated in one visit, and 98% were treated in 1 or 2 visits.

[37] Currently approved pursuant to the Paperwork Reduction Act of 1995.

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